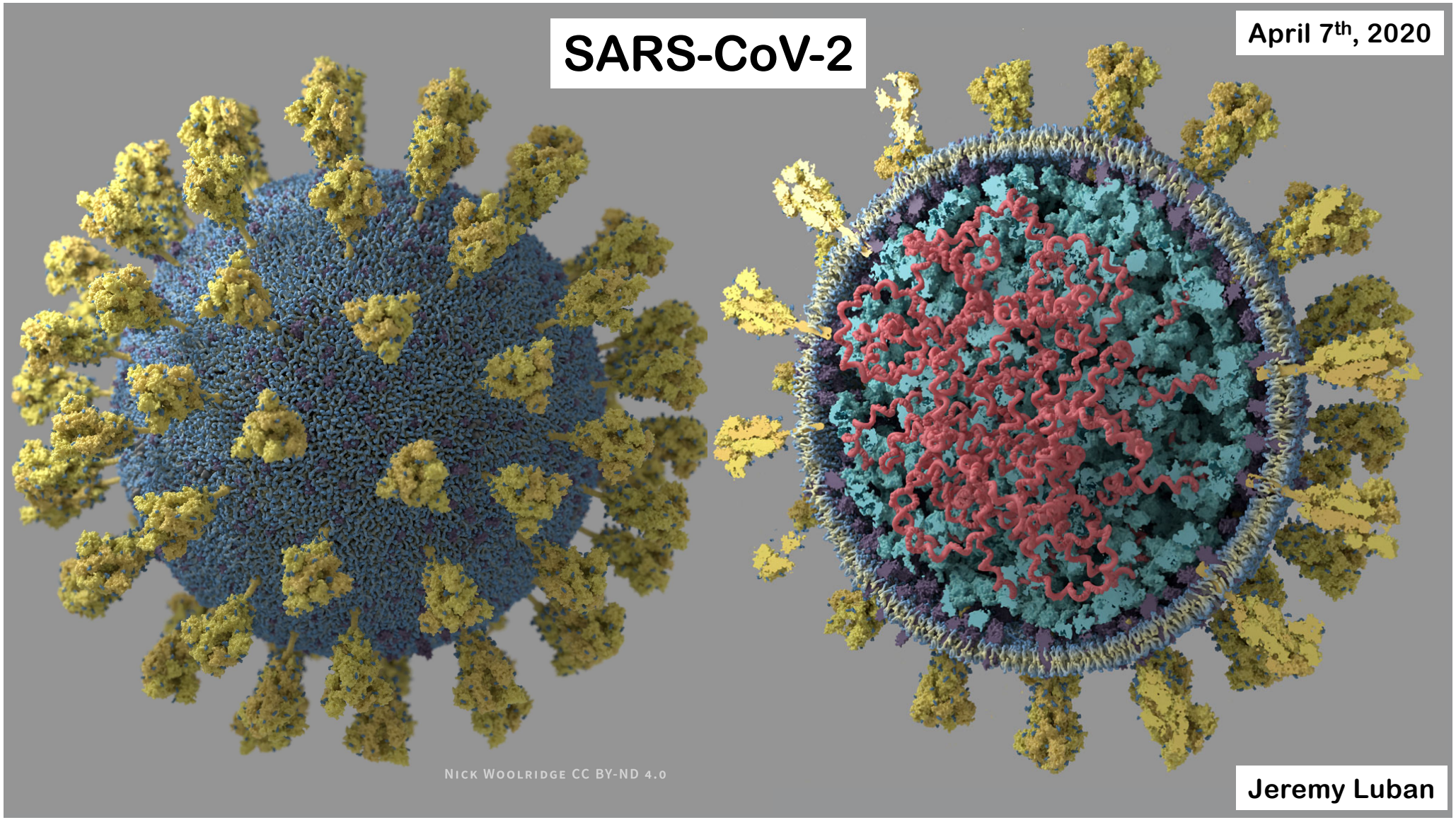
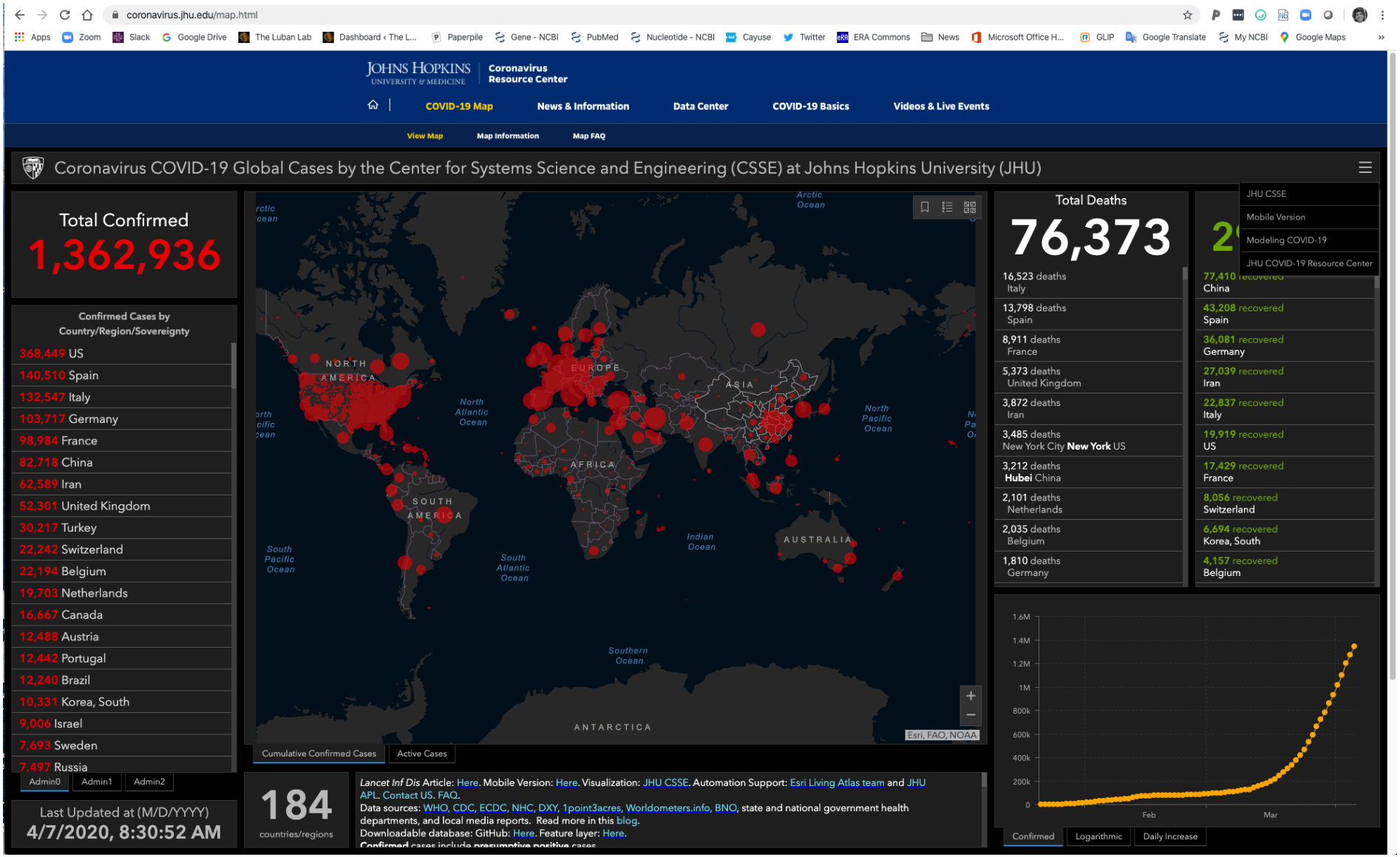
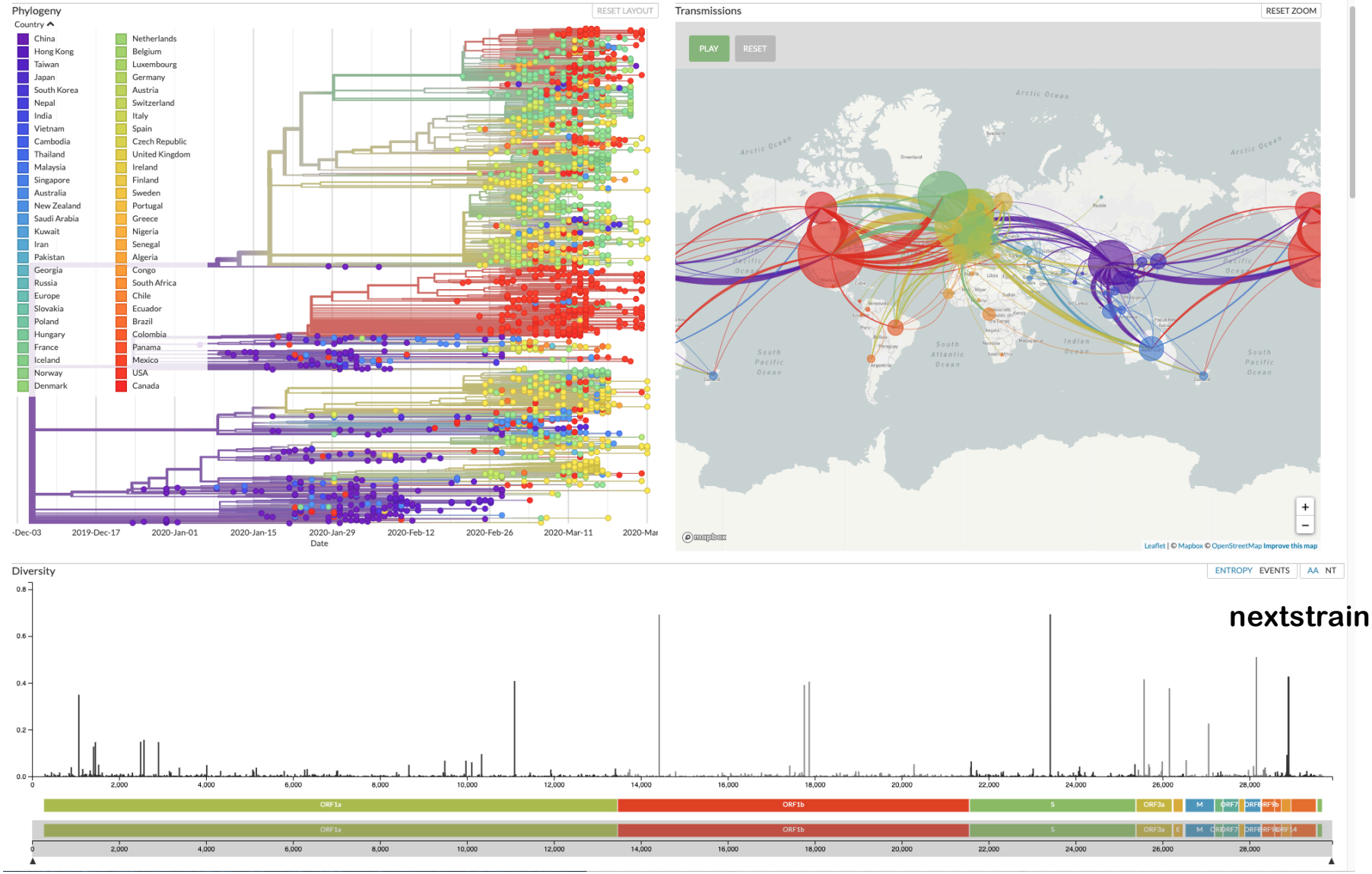
2020-04-07

SARS-CoV-2

Jeremy Luban
University of Massachusetts Medical School


SARS-CoV-2
April 7th, 2020
Nick Woolridge CC BY-ND 4.0
Jeremy Luban


coronavirus.jhu.edu/map.html
JOHNS HOPKINS UNIVERSITY & MEDICINE
Coronavirus Resource Center
COVID-19 Map
News & Information
Data Center
COVID-19 Basics
Videos & Live Events
View Map
Map Information
Map FAQ
Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU)
JHU CSSE
Mobile Version
Modeling COVID-19
JHU COVID-19 Resource Center
Total Confirmed
1,362,936
Confirmed Cases by Country/Region/Sovereignty
368,449 US
140,510 Spain
132,547 Italy
103,717 Germany
98,984 France
82,718 China
62,589 Iran
52,301 United Kingdom
30,217 Turkey
22,242 Switzerland
22,194 Belgium
19,703 Netherlands
16,667 Canada
12,488 Austria
12,442 Portugal
12,240 Brazil
10,331 Korea, South
9,006 Israel
7,693 Sweden
7,497 Russia
Admin0
Admin1
Admin2
Last Updated at (M/D/YYYY)
4/7/2020, 8:30:52 AM
NORTH AMERICA
EUROPE
ASIA
AFRICA
SOUTH AMERICA
AUSTRALIA
ANTARCTICA
Arctic Ocean
North Atlantic Ocean
North Pacific Ocean
South Pacific Ocean
South Atlantic Ocean
Indian Ocean
Southern Ocean
Esri, FAO, NOAA
Cumulative Confirmed Cases
Active Cases
184
countries/regions
Lancet Inf Dis Article: Here. Mobile Version: Here. Visualization: JHU CSSE. Automation Support: Esri Living Atlas team and JHU APL. Contact US. FAQ.
Data sources: WHO, CDC, ECDC, NHC, DXY, 1point3acres, Worldometers.info, BNO, state and national government health departments, and local media reports. Read more in this blog.
Downloadable database: GitHub: Here. Feature layer: Here.
Confirmed cases include presumptive positive cases
Total Deaths
76,373
16,523 deaths Italy
13,798 deaths Spain
8,911 deaths France
5,373 deaths United Kingdom
3,872 deaths Iran
3,485 deaths New York City New York US
3,212 deaths Hubei China
2,101 deaths Netherlands
2,035 deaths Belgium
1,810 deaths Germany
77,410 recovered China
43,208 recovered Spain
36,081 recovered Germany
27,039 recovered Iran
22,837 recovered Italy
19,919 recovered US
17,429 recovered France
8,056 recovered Switzerland
6,694 recovered Korea, South
4,157 recovered Belgium
1.6M
1.4M
1.2M
1M
800k
600k
400k
200k
0
Feb
Mar
Confirmed
Logarithmic
Daily Increase


Phylogeny
RESET LAYOUT
Country
China
Hong Kong
Taiwan
Japan
South Korea
Nepal
India
Vietnam
Cambodia
Thailand
Malaysia
Singapore
Australia
New Zealand
Saudi Arabia
Kuwait
Iran
Pakistan
Georgia
Russia
Europe
Slovakia
Poland
Hungary
France
Iceland
Norway
Denmark
Netherlands
Belgium
Luxembourg
Germany
Austria
Switzerland
Italy
Spain
Czech Republic
United Kingdom
Ireland
Finland
Sweden
Portugal
Greece
Nigeria
Senegal
Algeria
Congo
South Africa
Chile
Ecuador
Brazil
Colombia
Panama
Mexico
USA
Canada
-Dec-03
2019-Dec-17
2020-Jan-01
2020-Jan-15
2020-Jan-29
2020-Feb-12
2020-Feb-26
2020-Mar-11
2020-Mar
Date
Transmissions
RESET ZOOM
PLAY
RESET
Arctic Ocean
Greenland
Russia
South Pacific Ocean
South Atlantic Ocean
Indian Ocean
mapbox
Leaflet | © Mapbox © OpenStreetMap Improve this map
Diversity
ENTROPY
EVENTS
AA
NT
0.8
0.6
0.4
0.2
0.0
0
2,000
4,000
6,000
8,000
10,000
12,000
14,000
16,000
18,000
20,000
22,000
24,000
26,000
28,000
ORF1a
ORF1b
S
ORF3a
E
M
ORF7
ORF9b
ORF14
nextstrain.org

Wölfel, R., et al. (2020). Virological assessment of 9 hospitalized patients with COVID-2019. Nature. in press

Nasal swabs

average RNA load 7 x 10^5; max 7 x 10^8
17% virus positive in 1st week

Sputum

average RNA load 7 x 10^6; max 2 x 10^9
83% virus positive in 1st week

Virus isolation

None positive after day 8 or when viral load <10^6

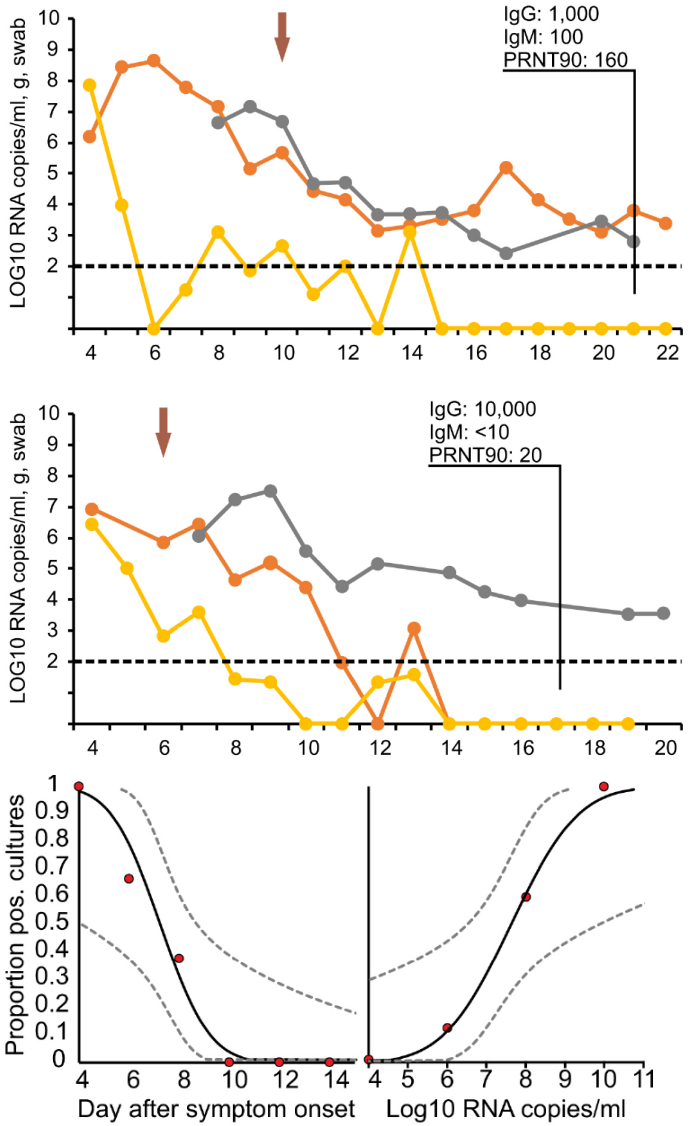
Virus replication in upper respiratory tract

sgRNA in swab

Pre-cleaved? point mutation in swab vs sputum

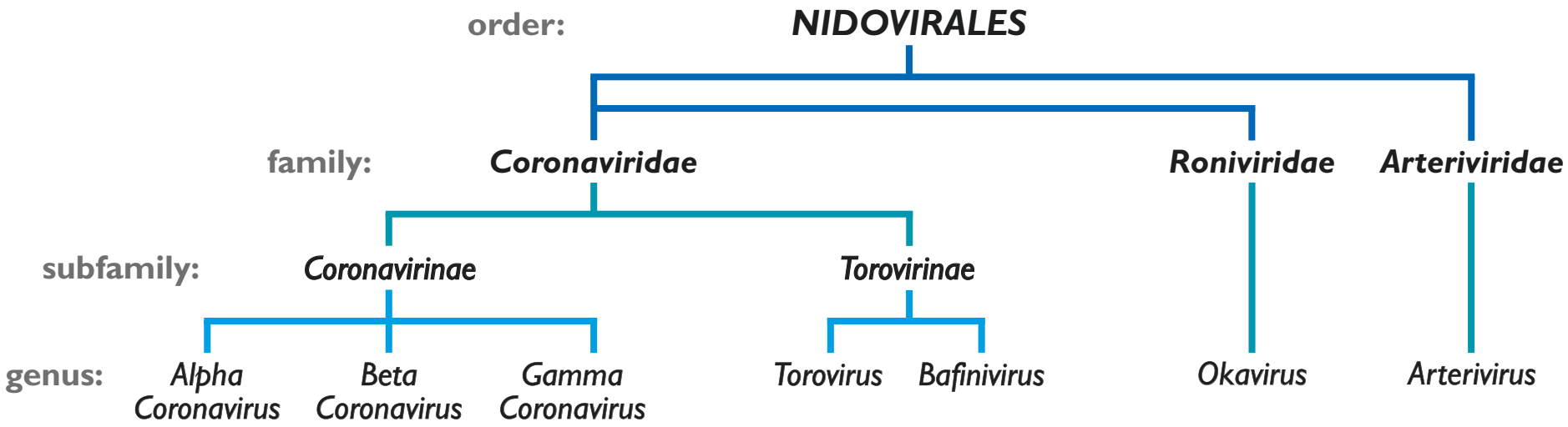
Seroconversion

50% + by day 7; 100% by day 14
all had neutralizing abs



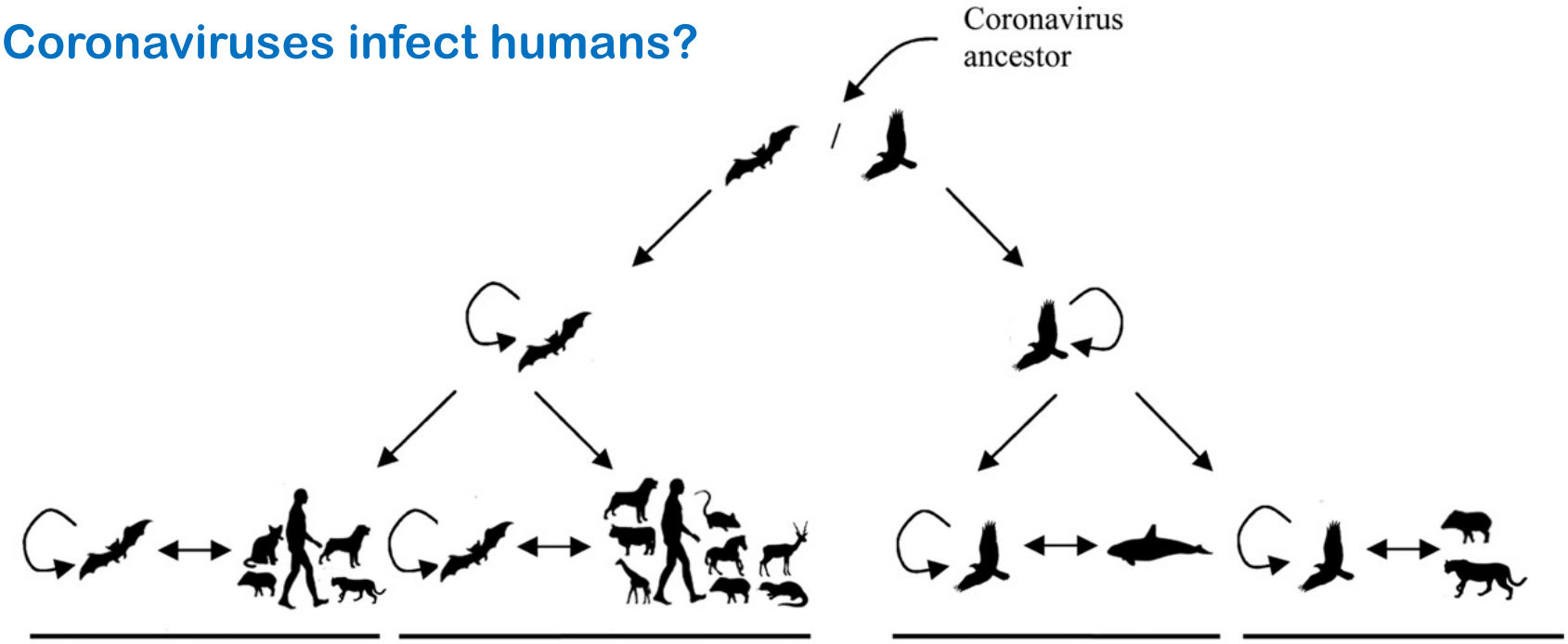
Where is SARS-CoV-2 within virus taxonomy?

SARS-CoV-2 is a Beta-Coronavirus in the order *Nidovirales*



produce 3' co-terminal nested subgenomic mRNA's during infection

Which Coronaviruses infect humans?



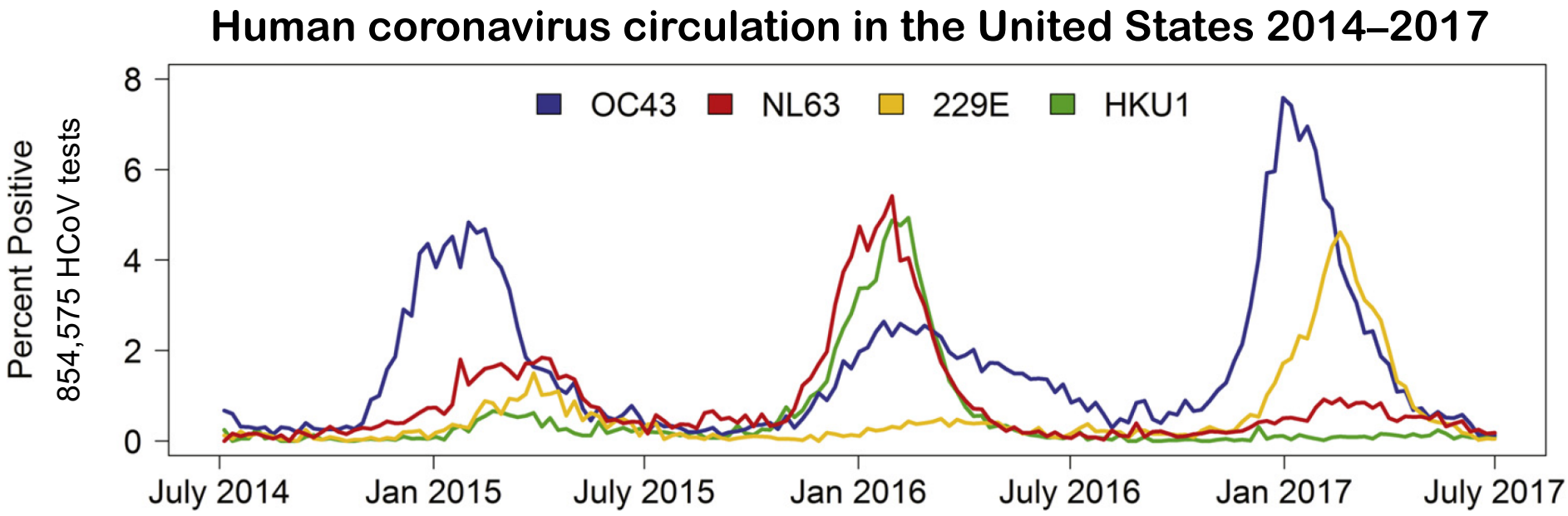
HCoV-NL63
HCoV-229E

HCoV-OC43
HCoV-HKU1
SARS-CoV
MERS-CoV
SARS-CoV-2

Sarbecovirus subgenus

J.Virol. 86:3995

Are coronaviruses endemic among humans?



Up to 30% of seasonal common cold

2-4 yr peaks

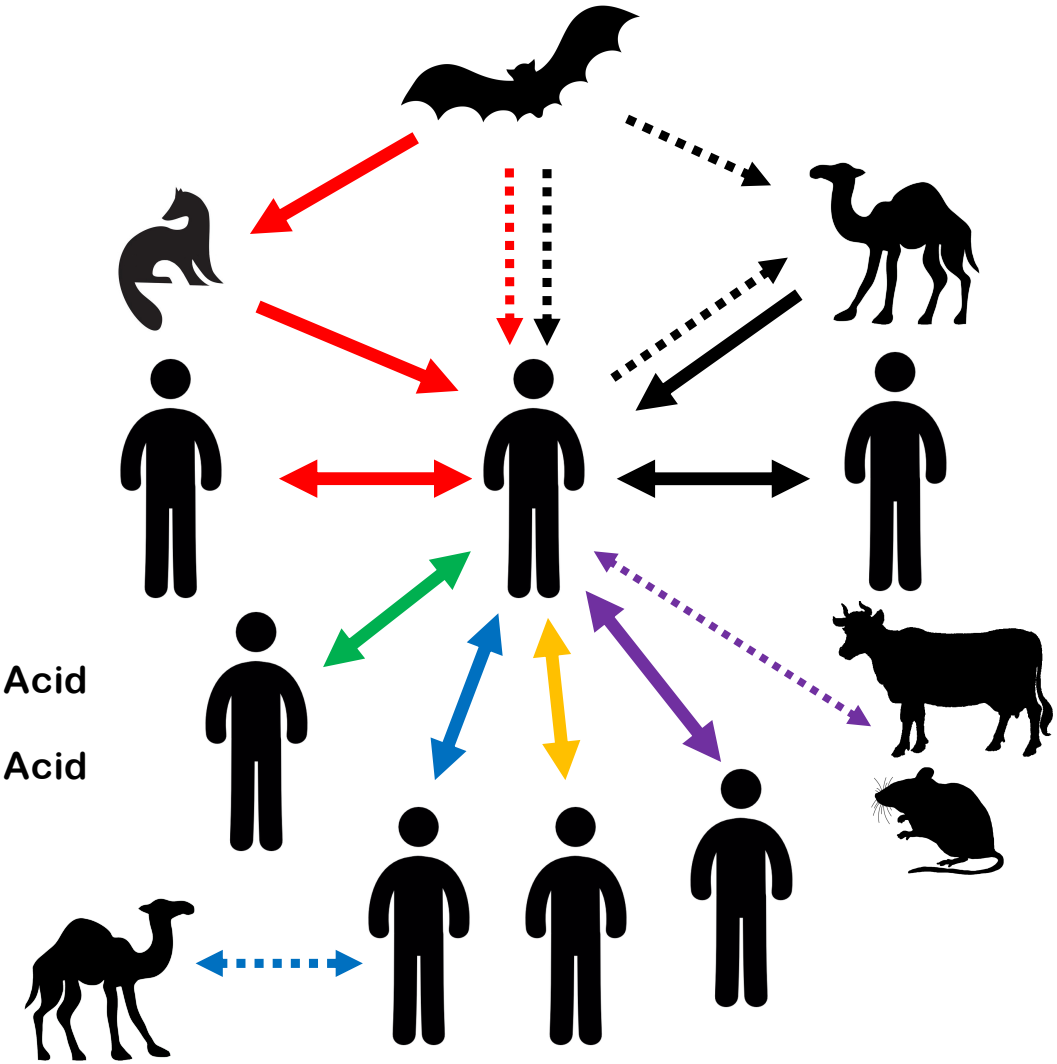
Why do they keep returning?

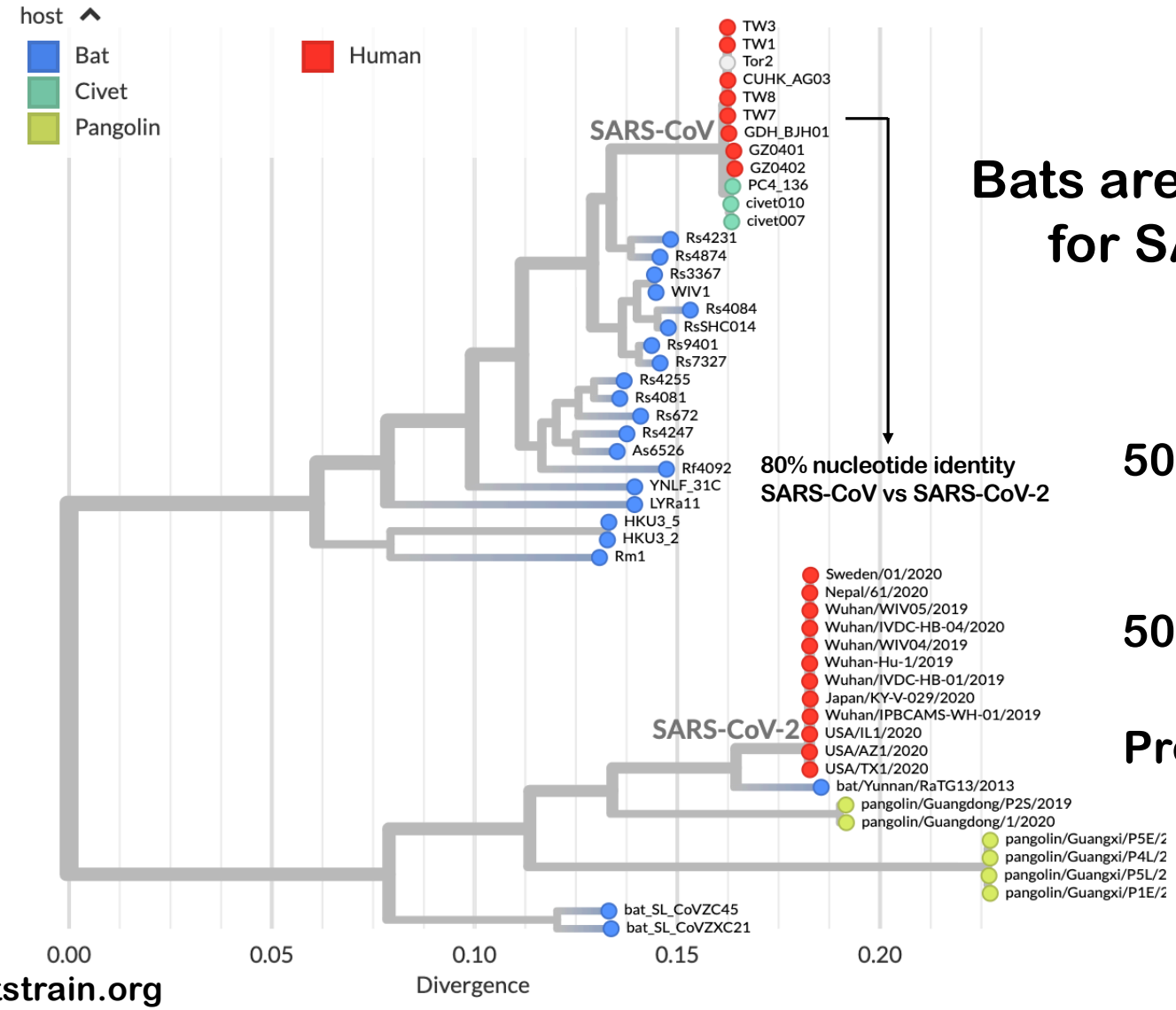
Weak immunity vs strain variants

J Clin Virol 101:52

Human coronavirus circulation & reservoirs pre-COVID-19

	MERS-CoV	DPP4
	SARS-CoV	ACE2
Circulate globally	HCoV-NL63	ACE2
Circulate globally	HCoV-HKU1	9-O-Ac-Sialic Acid
Common cold	HCoV-OC43	9-O-Ac-Sialic Acid
Common cold	HCoV-229E	APN





nextstrain.org

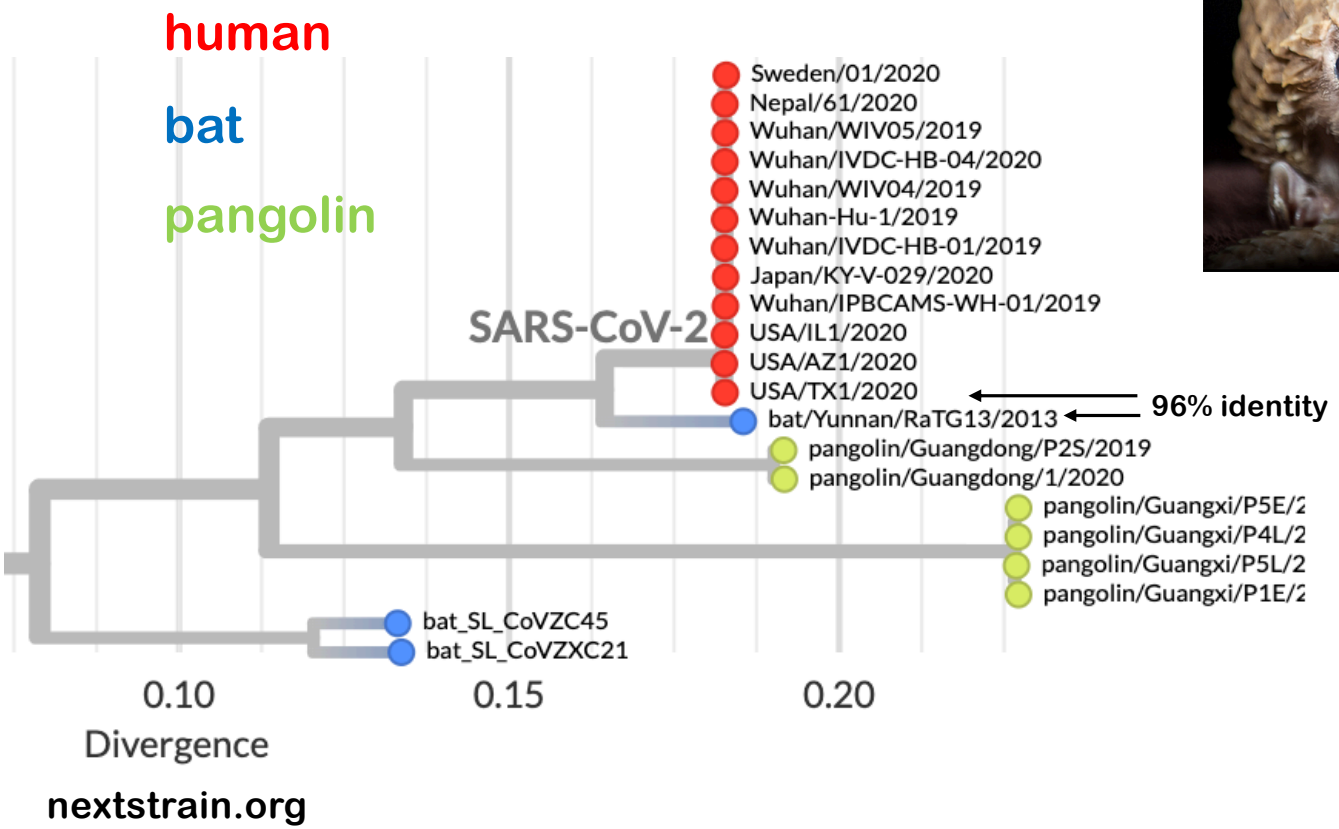
Bats are the main reservoir for SARS-like viruses

500 novel coronaviruses in bats in China

50 in the SARS family

Predicts future outbreaks

Bat is SARS-CoV-2 reservoir
pangolin possible intermediate



nextstrain.org

Overall, bat viruses closer to SARS-CoV-2 than are pangolin viruses

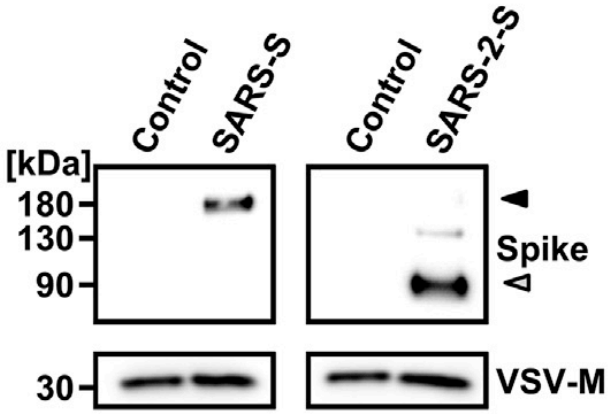
Critical residues in S protein are more similar between human and pangolin viruses

Pangolin ACE2 closer to human ACE2 than is bat ACE2

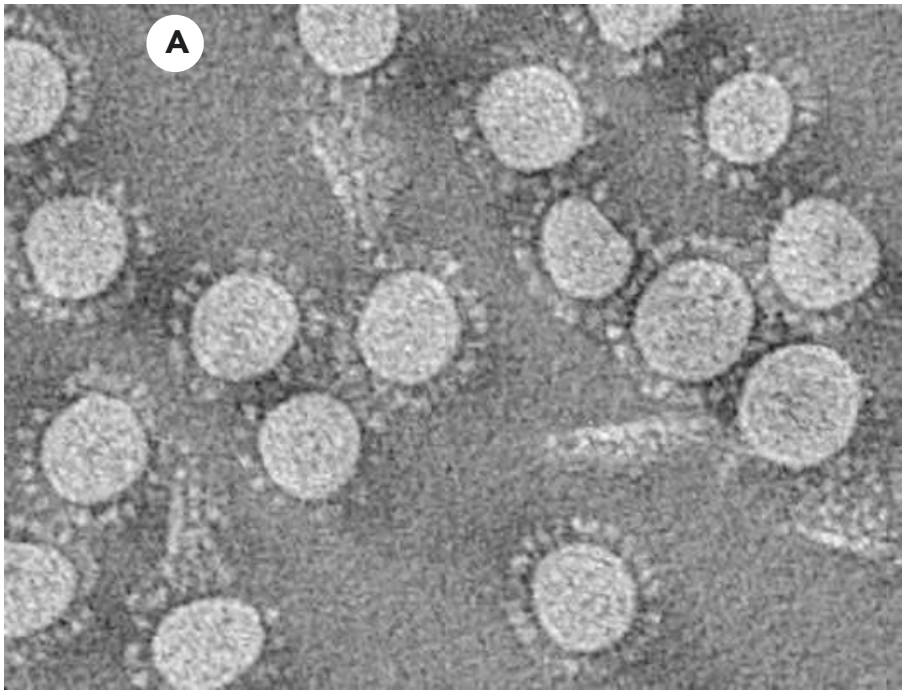
Some differences between SARS-CoV and SARS-CoV-2

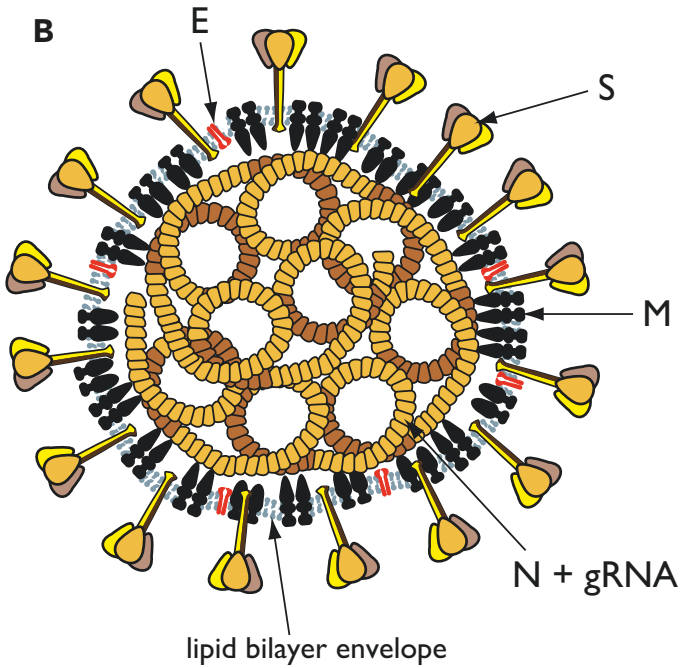
	SARS-CoV	SARS-CoV-2
Cases	8,096	1,346,299 (166x)
Deaths	774	74,679 (96x)
Asymptomatic infection	No	Yes (50%?)
Upper airway virus replication	No	Yes
Polybasic cleavage site in S protein	No	Yes

?

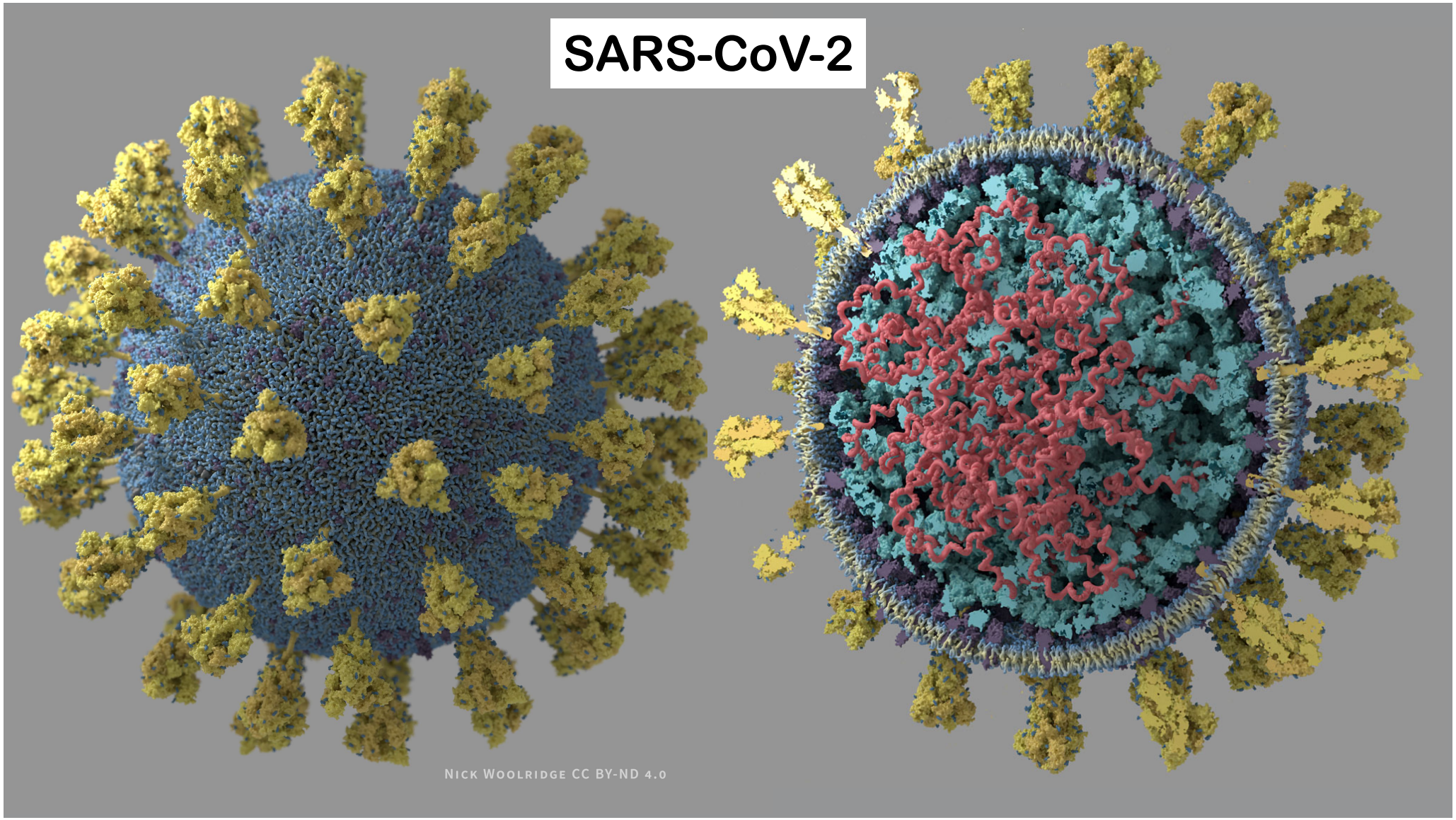


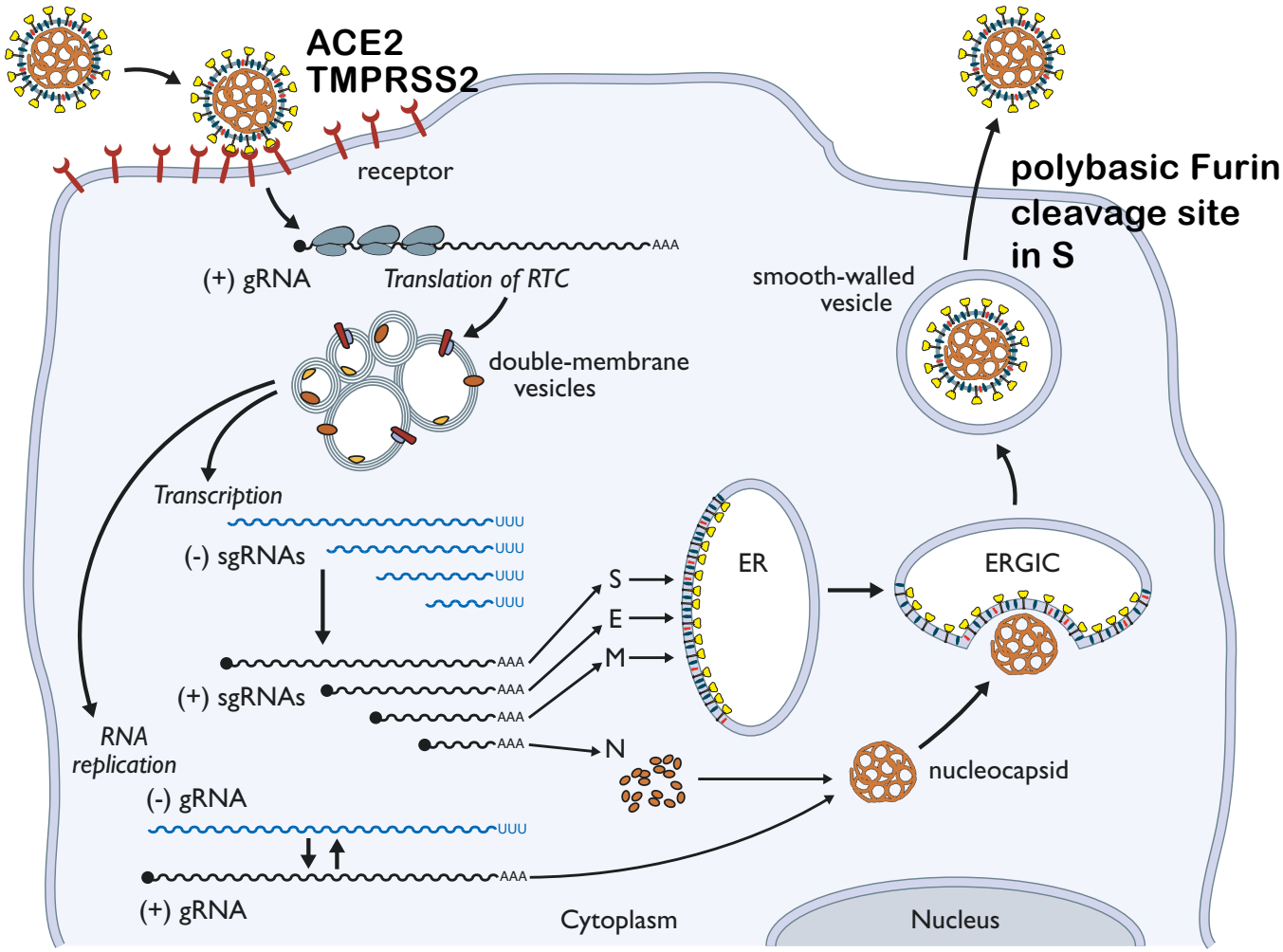
Cell in press
https://doi.org/10.1016/j.cell.2020.02.052





Fields Virology; Masters & Perlman

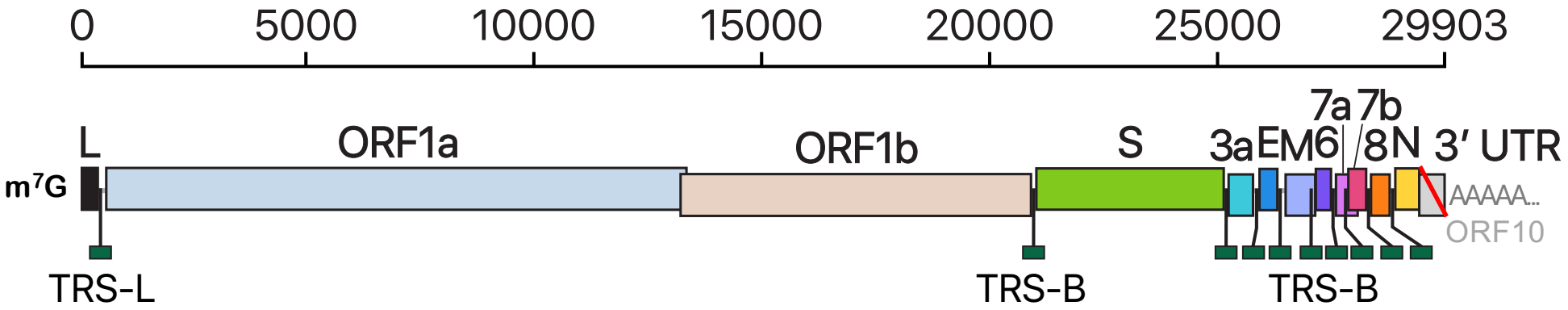

SARS-CoV-2
Nick Woolridge CC BY-ND 4.0



Lifecycle of SARS-CoV-2

Fields Virology; Masters & Perlman

SARS-CoV-2 genome: 30kB plus-sense RNA

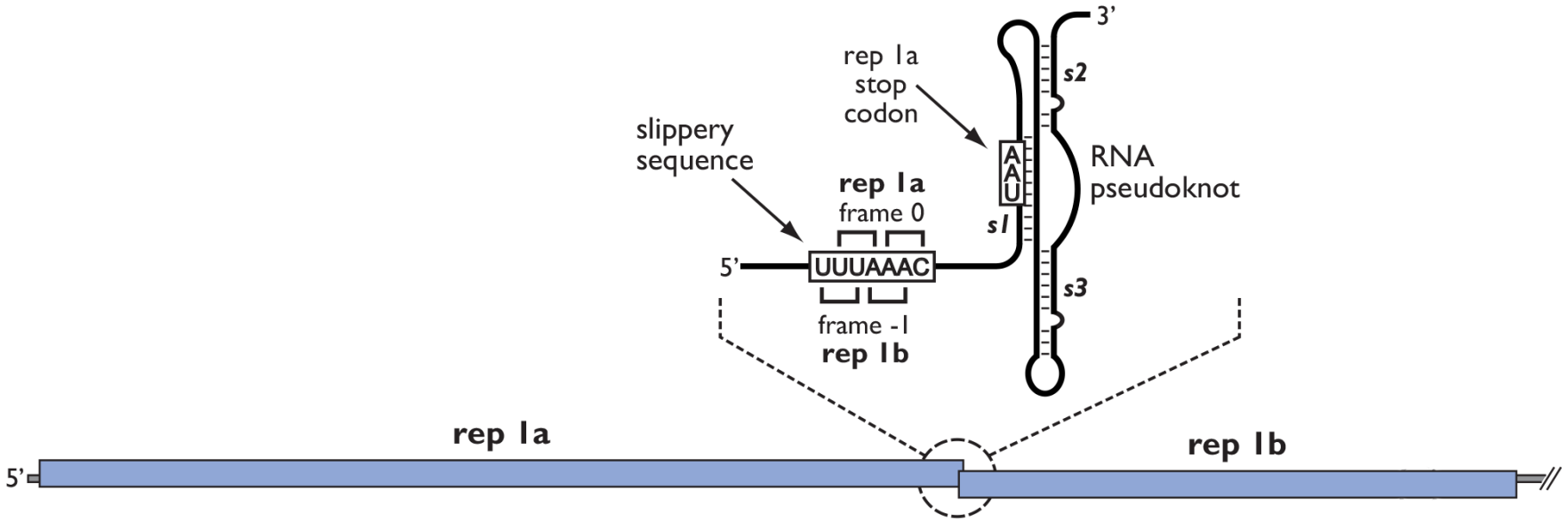


How does one RNA make 30 proteins in a eukaryotic cell?

- encodes 2 polyproteins
- encodes 2 proteases
- ribosomal frameshift
- discontinuous transcription/programmed recombination

https://doi.org/10.1101/2020.03.12.988865

Ribosomal frameshift produces pp1a + pp1ab

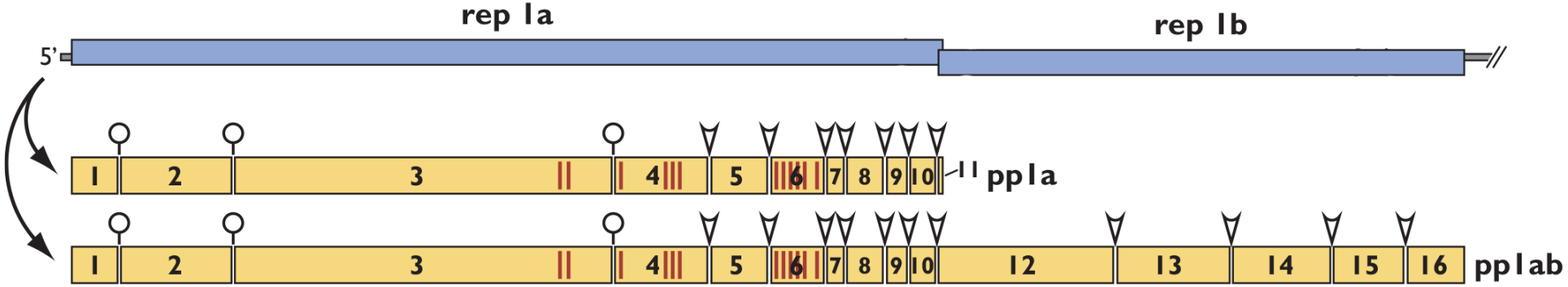


slippery sequence just before the replicase 1a stop codon

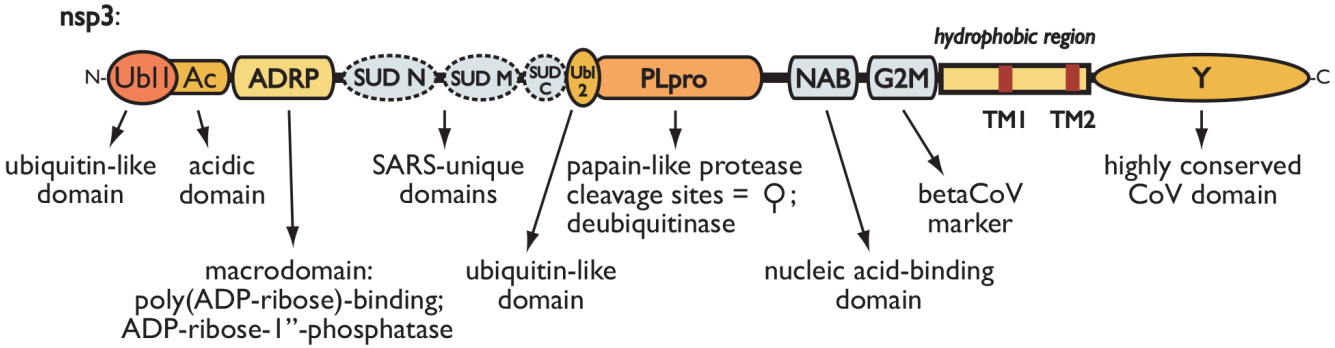
RNA stem-loop with pseudoknot

Fields Virology; Masters & Perlman

Two major polyproteins: pp1a + pp1ab



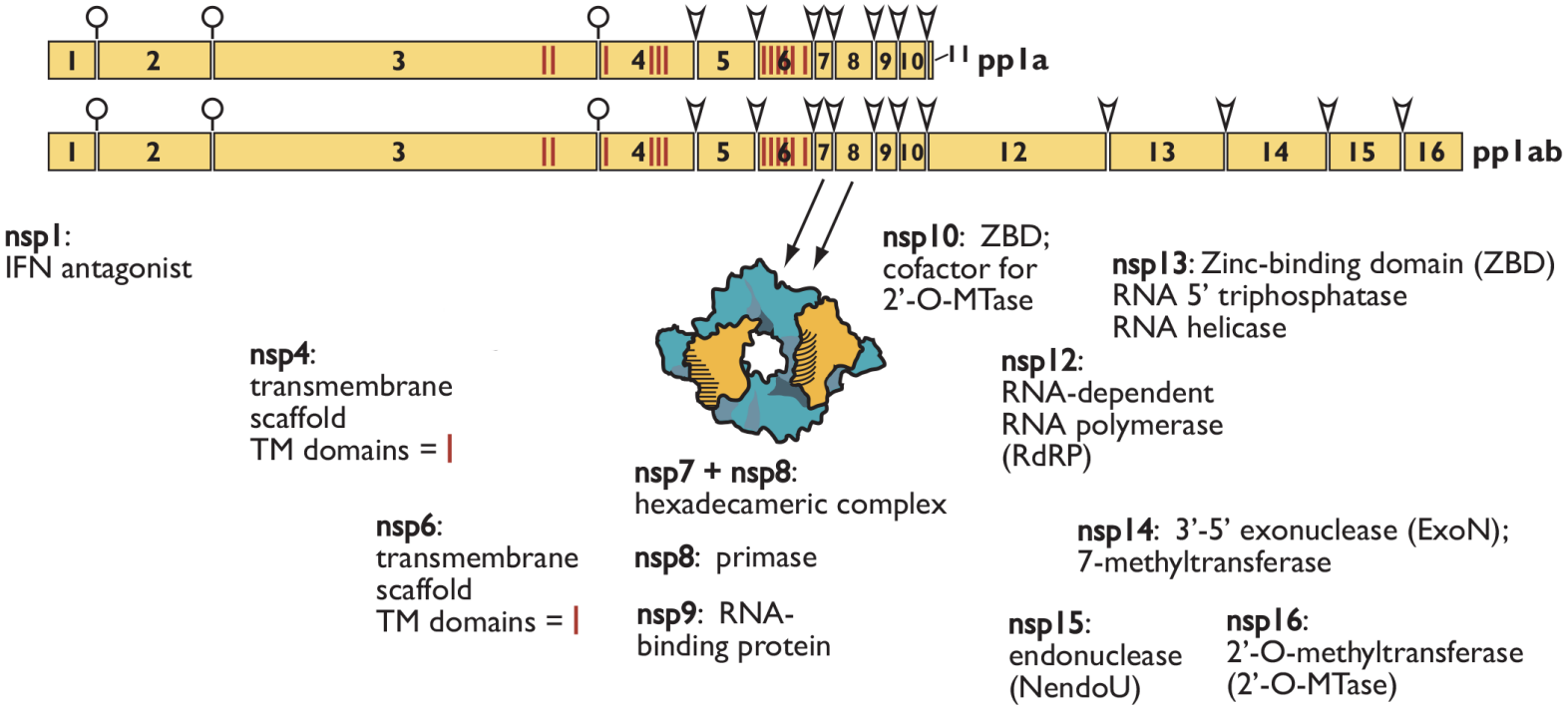
Two proteases



nsp5:
main protease
(Mpro, 3CL)
cleavage sites = ∀

Fields Virology; Masters & Perlman

SARS-CoV-2 has an amazing set of proteins



Antagonists of the immune system (e.g., 2'-O-MTase; nsp16)

RNA replication machinery (RdRP; nsp12)

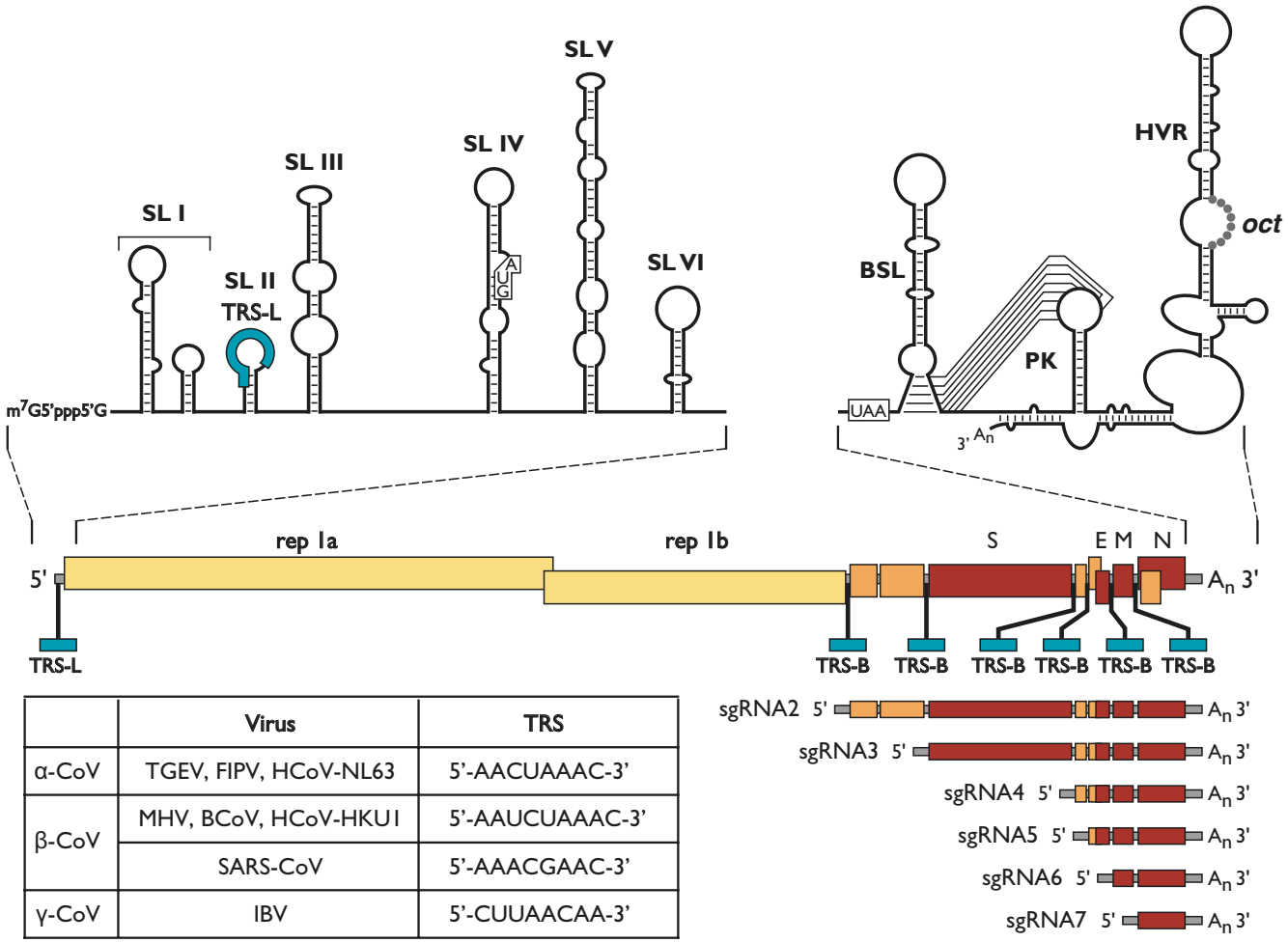
Replication proof-reading (3'-5' exonuclease; nsp14)

RNA metaboblism in the cytoplasm (7-methyltransferase; nsp14)

Fields Virology; Masters & Perlman

A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing

David E. Gordon[1,2,3,4], Gwendolyn M. Jang[1,2,3,4], Mehdi Bouhaddou[1,2,3,4], Jiewei Xu[1,2,3,4], Kirsten Obernier[1,2,3,4], Matthew J. O'Meara[5], Jeffrey Z. Guo[1,2,3,4], Danielle L. Swaney[1,2,3,4], Tia A. Tummino[1,2,6], Ruth Hüttenhain[1,2,3,4], Robyn M. Kaake[1,2,3,4], Alicia L. Richards[1,2,3,4], Beril Tutuncuoglu[1,2,3,4], Helene Foussard[1,2,3,4], Jyoti Batra[1,2,3,4], Kelsey Haas[1,2,3,4], Maya Modak[1,2,3,4], Minkyu Kim[1,2,3,4], Paige Haas[1,2,3,4], Benjamin J. Polacco[1,2,3,4], Hannes Braberg[1,2,3,4], Jacqueline M. Fabius[1,2,3,4], Manon Eckhardt[1,2,3,4], Margaret Soucheray[1,2,3,4], Melanie J. Bennett[1,2,3,4], Merve Cakir[1,2,3,4], Michael J McGregor[1,2,3,4], Qiongyu Li[1,2,3,4], Zun Zar Chi Naing[1,2,3,4], Yuan Zhou[1,2,3,4], Shiming Peng[1,2,6], Ilsa T. Kirby[1,4,7], James E. Melnyk[1,4,7], John S. Chorba[1,4,7], Kevin Lou[1,4,7], Shizhong A. Dai[1,4,7], Wenqi Shen[1,4,7], Ying Shi[1,4,7], Ziyang Zhang[1,4,7], Inigo Barrio-Hernandez[8], Danish Memon[8], Claudia Hernandez-Armenta[8], Christopher J.P. Mathy[1,2,9,10], Tina Perica[1,2,9], Kala B. Pilla[1,2,9], Sai J. Ganesan[1,2,9], Daniel J. Saltzberg[1,2,9], Rakesh Ramachandran[1,2,9], Xi Liu[1,2,6], Sara B. Rosenthal[11], Lorenzo Calviello[12], Srivats Venkataramanan[12], Yizhu Lin[12], Stephanie A. Wankowicz[1,9,13], Markus Bohn[6], Raphael Trenker[14], Janet M. Young[15], Devin Cavero[16,3], Joe Hiatt[16,3], Theo Roth[16,3], Ujjwal Rathore[16,3], Advait Subramanian[1,17], Julia Noack[1,17], Mathieu Hubert[18], Ferdinand Roesch[19], Thomas Vallet[19], Björn Meyer[19], Kris M. White[20], Lisa Miorin[20], David Agard[1,21], Michael Emerman[22], Davide Ruggero[23,24,4], Adolfo García-Sastre[20], Natalia Jura[1,14,4], Mark von Zastrow[1,2,4,25], Jack Taunton[1,2,4], Olivier Schwartz[18], Marco Vignuzzi[19], Christophe d'Enfert[26], Shaeri Mukherjee[1,17], Matt Jacobson[6], Harmit S. Malik[15], Danica G. Fujimori[1,4,6], Trey Ideker[27], Charles S. Craik[6,24], Stephen Floor[12,24], James S. Fraser[1,2,9], John Gross[1,2,6], Andrej Sali[1,2,6,9], Tanja Kortemme[1,9,10,2], Pedro Beltrao[8], Kevan Shokat[1,4,7], Brian K. Shoichet[1,2,6], Nevan J. Krogan[1,2,3,4]

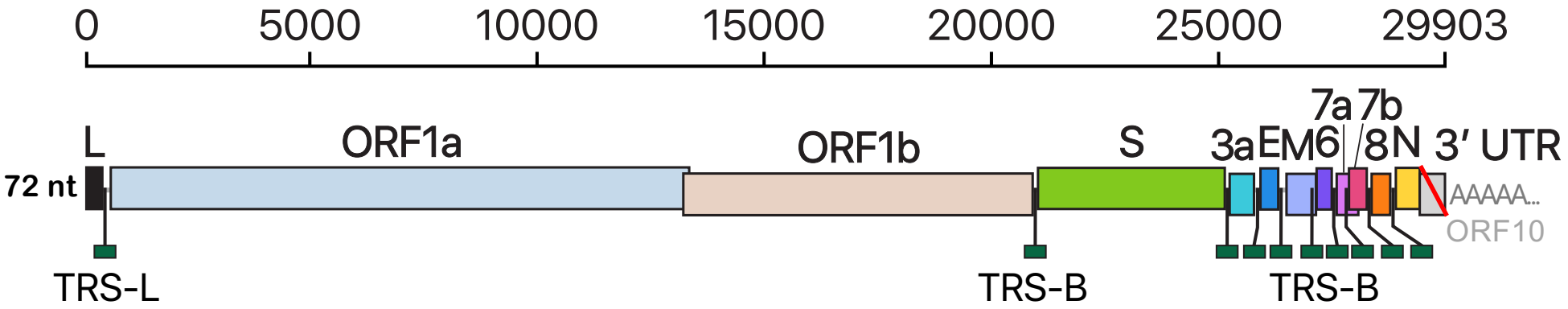


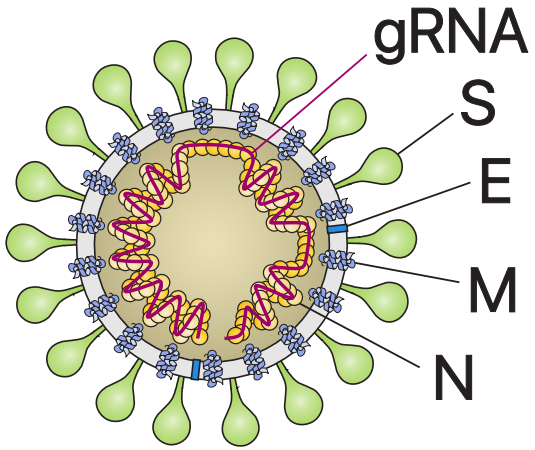
	Virus	TRS
α-CoV	TGEV, FIPV, HCoV-NL63	5'-AACUAAAC-3'
β-CoV	MHV, BCoV, HCoV-HKU1	5'-AAUCUAAAC-3'
	SARS-CoV	5'-AAACGAAC-3'
γ-CoV	IBV	5'-CUUAACAA-3'

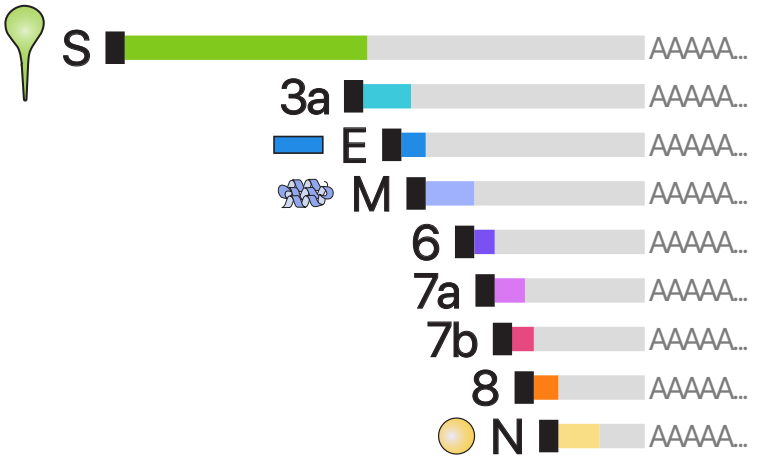
SARS-CoV-2? **5'-AAACGAAC-3'**

Fields Virology; Masters & Perlman

SARS-CoV-2 transcripts based on direct RNA-Seq

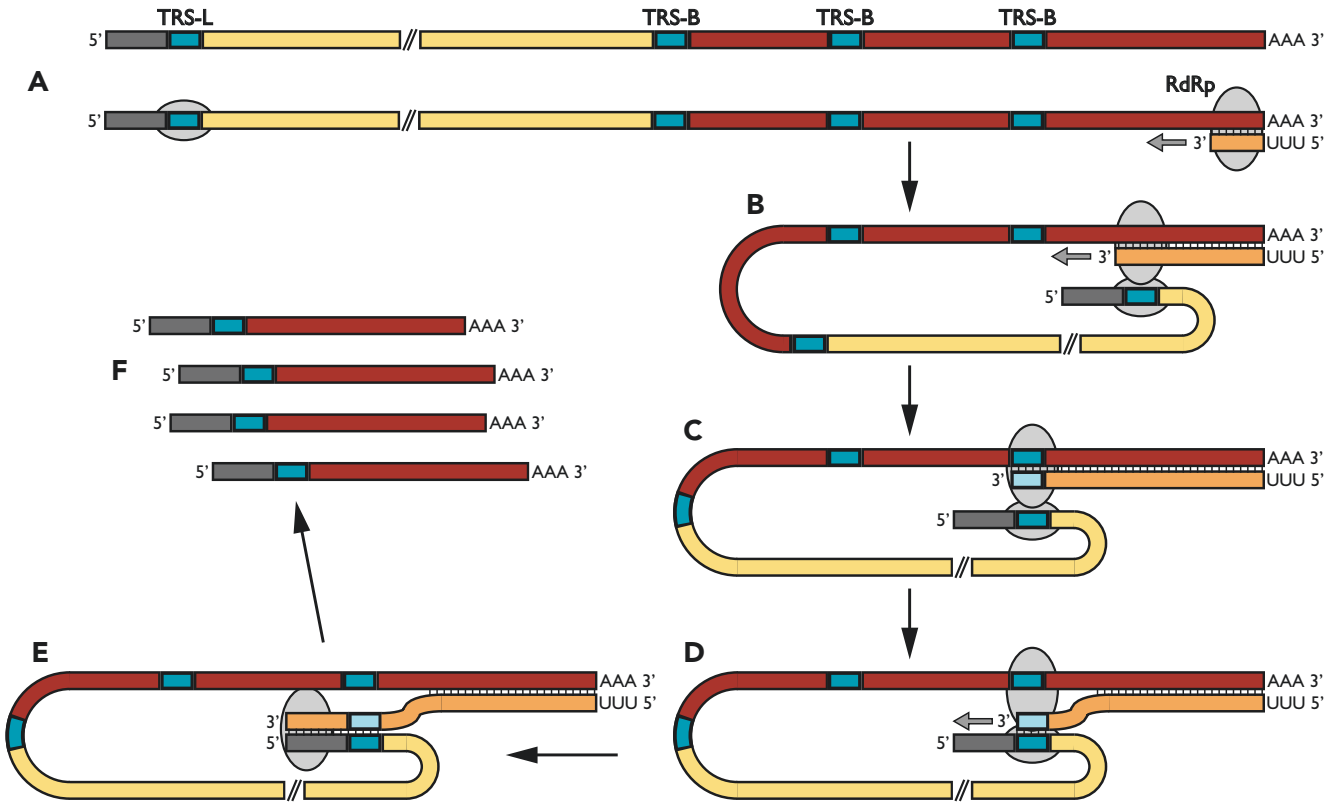






https://doi.org/10.1101/2020.03.12.988865

Leader to body fusion during negative-strand synthesis



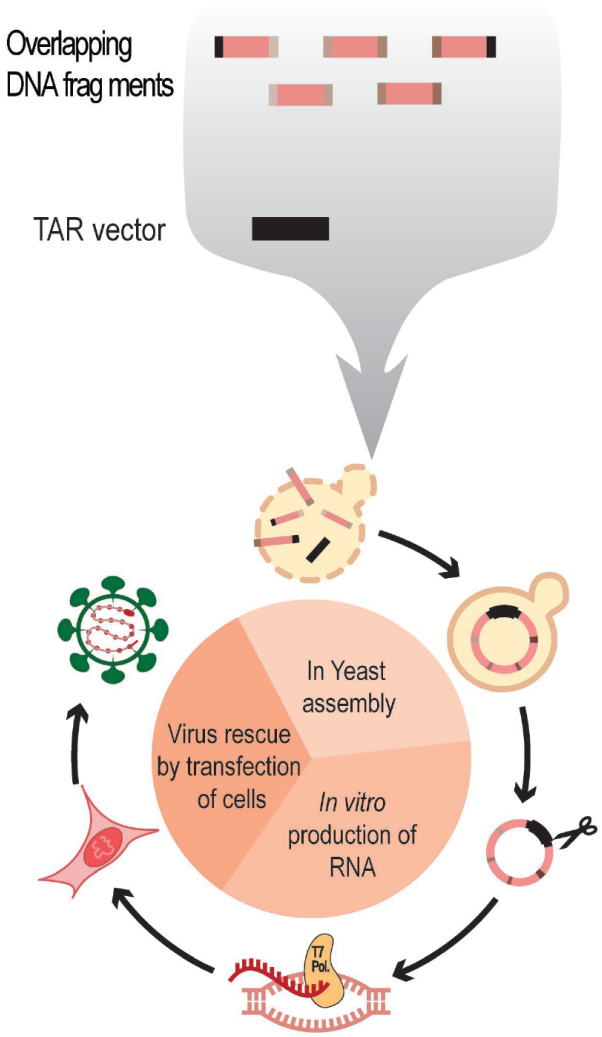
TRS: transcription-regulating sequen

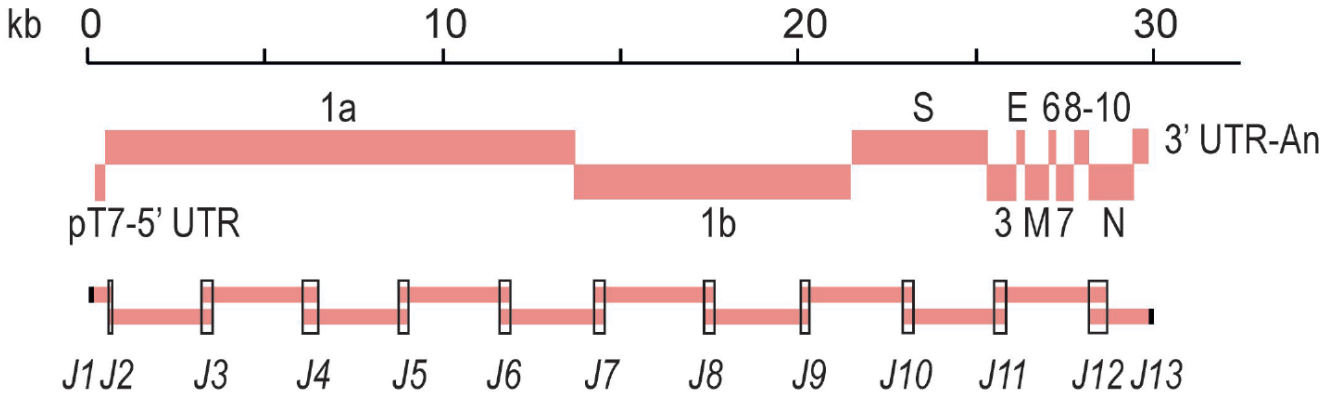
L: leader

B: body

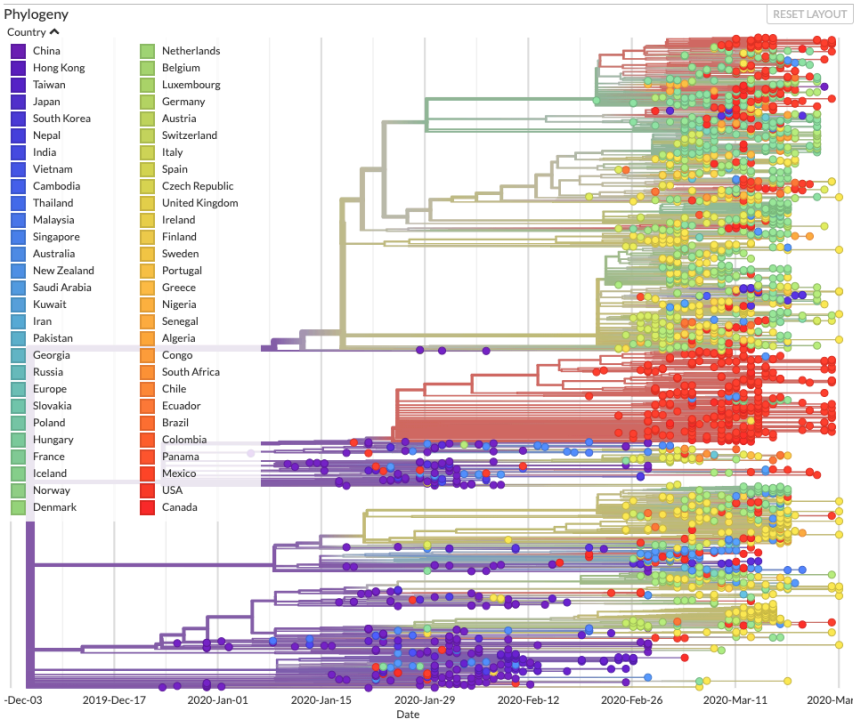
Fields Virology; Masters & Perlman

In the age of CRISPR nothing trumps the awesome power of yeast genetics





Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform
bioRxiv https://doi.org/10.1101/2020.02.21.959817


Phylogeny
RESET LAYOUT
Country
China
Hong Kong
Taiwan
Japan
South Korea
Nepal
India
Vietnam
Cambodia
Thailand
Malaysia
Singapore
Australia
New Zealand
Saudi Arabia
Kuwait
Iran
Pakistan
Georgia
Russia
Europe
Slovakia
Poland
Hungary
France
Iceland
Norway
Denmark
Netherlands
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Germany
Austria
Switzerland
Italy
Spain
Czech Republic
United Kingdom
Ireland
Finland
Sweden
Portugal
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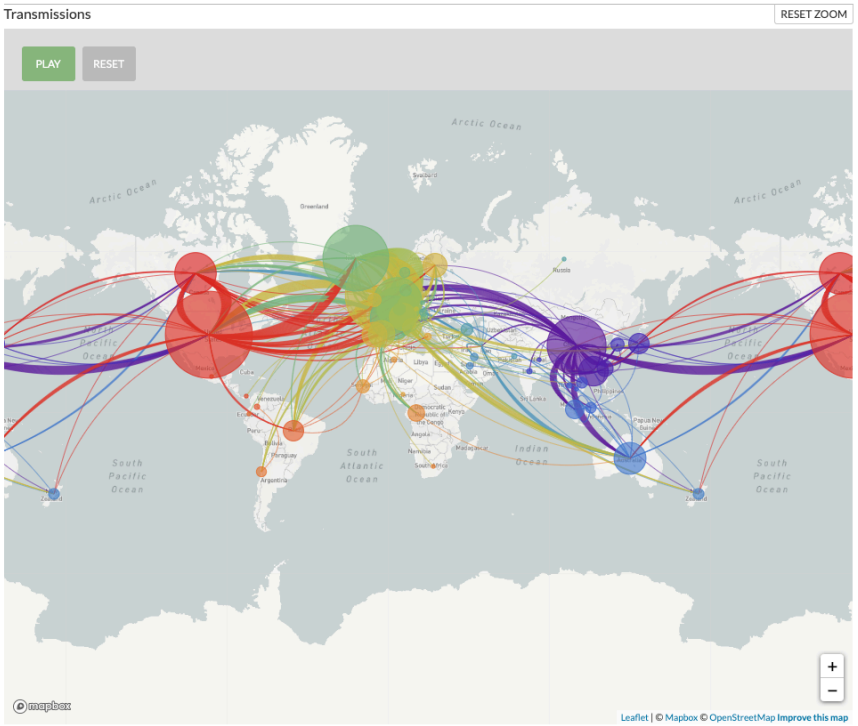
2020-Mar-11
2020-Mar
Date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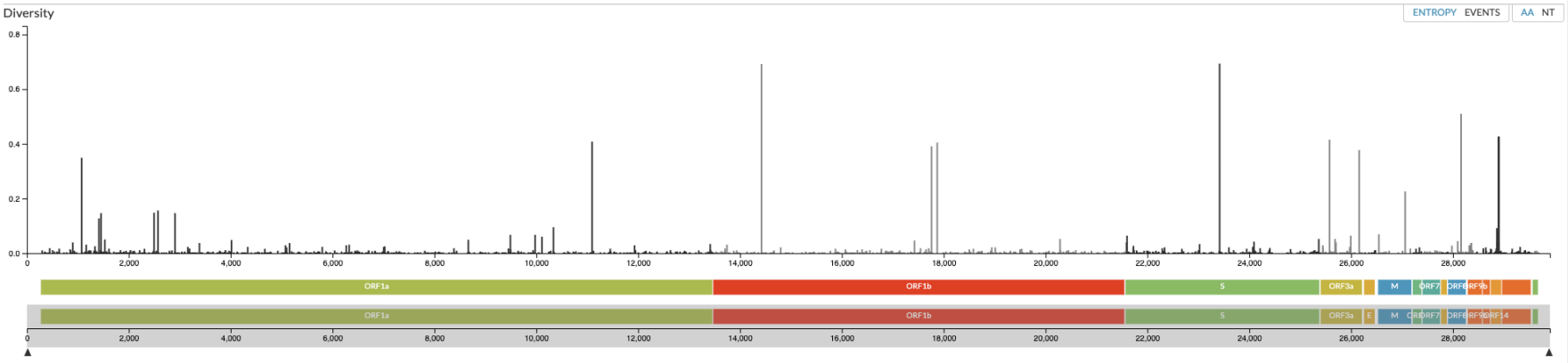
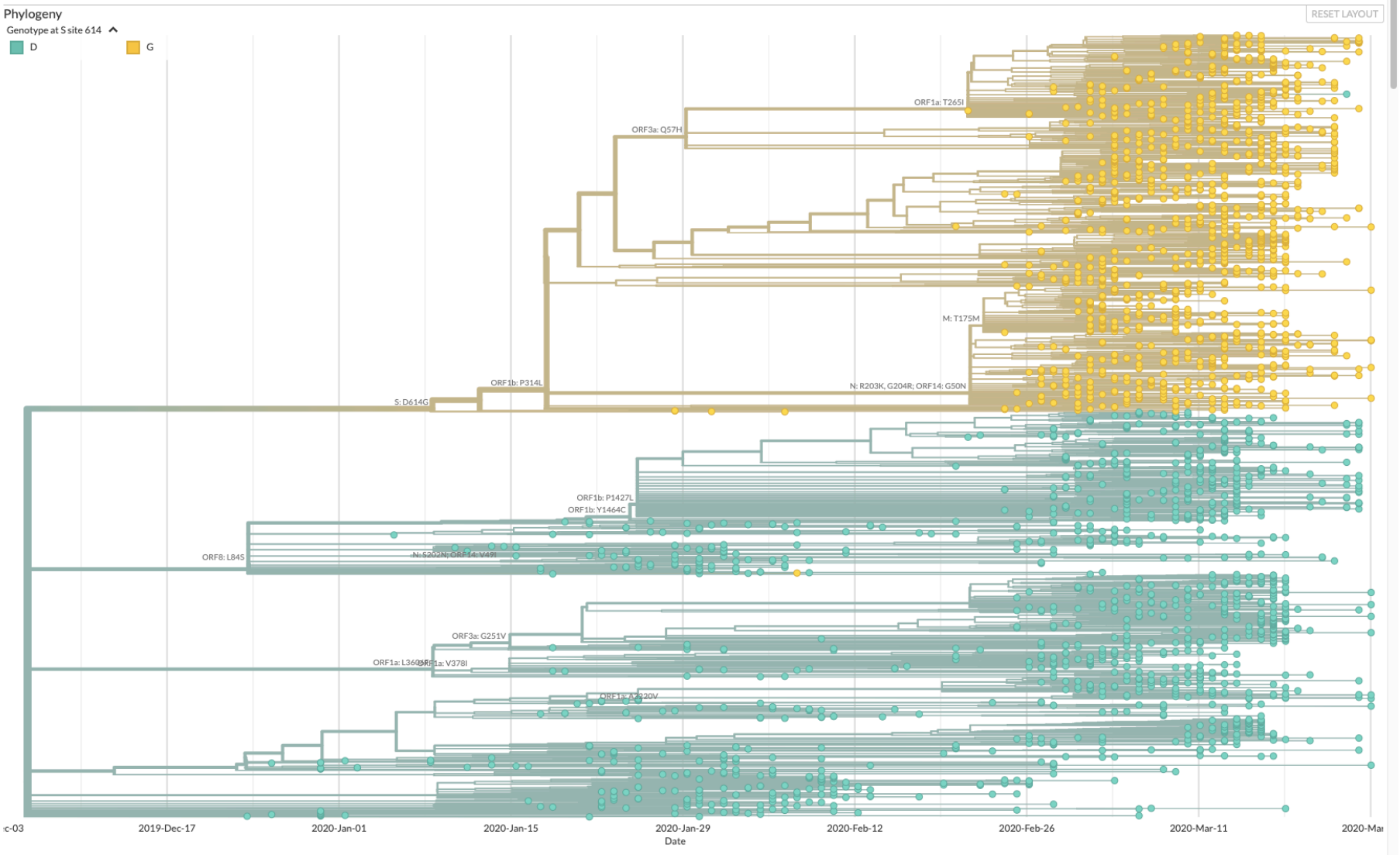
RESET
Arctic Ocean
Greenland
Russia
South Pacific Ocean
South Atlantic Ocean
Indian Ocean
mapbox
Leaflet | © Mapbox © OpenStreetMap Improve this map


Diversity
ENTROPY
EVENTS
AA
NT
0.8
0.6
0.4
0.2
0.0
0
2,000
4,000
6,000
8,000
10,000
12,000
14,000
16,000
18,000
20,000
22,000
24,000
26,000
28,000
ORF1a
ORF1b
S
ORF3a
M
ORF7
ORF9b

Showing 2649 of 2649 genomes sampled between Dec 2019 and Mar 2020.



Do sequence variants influence transmissibility or clinical outcome?

Viral load testing

Illumina sequencing

Long-read sequencing

Sequence analysis: SNPs, recombinants, haplotypes

Phenotypic analysis of isolated mutants in full virus, replicons, etc.